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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,273	03/25/2005	Gautam Vinod Daftary	24439.US	2139

7590 03/14/2008
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EXAMINER

STONE, CHRISTOPHER R

ART UNIT	PAPER NUMBER
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1614

MAIL DATE	DELIVERY MODE
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03/14/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/529,273	Applicant(s) DAFTARY ET AL.	
	Examiner CHRISTOPHER R. STONE	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27, 29-50 and 52 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27, 29-50 and 52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 11, 2008 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 29, 31-50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cserhati and Hollo) in view of (Links and Lewis) further in view of Zmitek et al (US Patent 5840714).

Cserhati and Hollo teaches a composition comprising cyclophosphamide (also known as cytoxan, i.e. an oxazaphosphorine of the formula of claim 27), hydroxypropyl- β -cyclodextrin (an etherified β -cyclodextrin), and water (p.70, 1st column, lines 28-34, 2nd column, lines 3-6 and p.71, Table 1, Number 16) Cyclophosphamide is taught to complex with hydroxypropyl- β -cyclodextrin (p. 72, left column, paragraph 3). Cserhati and Hollo further discloses that cyclodextrins increase the stability of guest molecules (p. 70, 1st column, line 4 and 5 and p.71, Table 1, Number 16.) Cserhati and Hollo does not disclose a pharmaceutical composition comprising the aqueous complexed hydroxypropyl- β -cyclodextrin/cyclophosphamide and mesna. Zmitek et al teaches pharmaceutical compositions comprising β -cyclodextrins complexed with an active agent, for instance piroxicam, ibuprofen and ibuprofen. In each of these cases the complex is taught to be less toxic than the active agent alone (column 2, line 66 through column 3, line 36). Links and Lewis discloses that mesna is a commonly used chemoprotective agent (i.e. protects against the known toxicities of the drugs) in patients receiving ifosfamide and cyclophosphamide (p.305, 2nd column, lines 1-3.) Therefore it would have been obvious to someone of ordinary skill in the art at the time of the instant invention, motivated by the desire to treat oxazaphosphorine-induced toxicity, to add mesna to the known aqueous hydroxypropyl- β -cyclodextrin/cyclophosphamide complex of Cserhati and Hollo since β -cyclodextrin-drug

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complexes were known to be less toxic than the active drug alone and mesna was a known chemoprotectant, commonly administered with cyclophosphamide, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success. Additionally, it would have been obvious to a person of ordinary skill in the art at the time of the instantly claimed invention to prepare the composition by mixing the components, i.e. by adding cyclophosphamide and mesna (as such or as an aqueous solution optionally containing a etherified β -cyclodextrin) to an aqueous solution of hydroxypropyl- β -cyclodextrin and optionally making up the volume with water.

The prior art renders the instantly claimed composition obvious to one of ordinary skill in the art at time of the instantly claimed invention and the optimization of composition components would have been obvious as well. Optimization of the molar substitution of Hydroxypropyl- β -cyclodextrin content and substitution would have been desired to acquire favorable complex formation. Optimization of oxazaphosphorine concentration would have been desired for optimal therapeutic effect. Optimization of the oxazaphosphorine to mesna ratio would have been desired to ensure optimal therapeutic effect with minimal urotoxicity.

The addition of parenteral additives to the composition at any step in the preparation would have been obvious to one of ordinary skill in the art at the time of the invention. The addition of additives such as buffers, diluents and chelators would have been desired to adjust the pH, to maintain the pH, to adjust the volume, to adjust the concentration, and to further increase stability and is common place in the pharmaceutical art.

Filter sterilizing the composition, aseptically filling it into sterile containers and sealing the containers would have been obvious to one of ordinary skill in the art at the time of the invention. Sterility would have been desired to avoid infection caused by contaminants in the composition. Using filter sterilization would have been particularly desirable since other sterilization techniques involve heating, which may deteriorate composition components.

Ifosfamide and cyclophosphamide were commonly used cancer drugs at the time of the invention. Therefore it would have been obvious to one of ordinary skill at the time of the invention to use the instantly claimed composition to treat a malignant disease because the therapeutically active oxazaphosphorine compounds were already commonly used for this purpose.

Claim 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cserhati and Hollo), in view of (Links and Lewis), Zmitek et al (US Patent 5840714) and (Baumann and Preiss).

Cserhati and Hollo, Links and Lewis and Zmitek et al (US Patent 5840714) disclose the aforementioned inventions, but they do not disclose the composition of the instantly claimed invention comprising ifosfamide. However, the composition of the instantly claimed invention comprising the oxazaphosphorine compound cyclophosphamide is disclosed. Baumann and Preiss discloses that cyclophosphamide and ifosfamide are the two most commonly used oxazaphosphorine compounds (p. 174, 1st column, lines 7-8.) The two compounds are isomers and share a very similar structure. Thus it would have been obvious to one of ordinary skill in the art at the time

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of the instant invention to use either oxazaphosphorine compound (cyclophosphamide or ifosfamide) in the composition of Cserhati and Hollo and to add mesna, since both compounds cause bladder toxicity. Thus resulting in the practice of the claimed invention with a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER R. STONE whose telephone number is (571)270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614